REMARKS

Claims 1, 4 to 9, 11, 18, 27, 38 and 66 to 88 are pending. Claims 1, 4, 27, 38, 70, 71, 75, 77 to 85 have been amended, and new claims 89 to 104 have been added herein. Following entry of the amendments, claims 1, 4 to 9, 11, 18, 27, 38 and 66 to 104 will be under examination.

Regarding the Amendments

Claims 1 and 71 have been amended to indicate that the claimed isolated nucleic acid molecule encodes a NAC polypeptide that contains an NB-ARC domain. Support for this amendment to claims 1 and 71 can be found throughout the specification, for example, at page 13, lines 29-35, and at page 82, lines 22-31, which indicates that a NAC NB-ARC domain demonstrates a strong ability to homodimerize.

Claim 4 has been rewritten in independent form. Support for the amendment to claim 4 can be found, for example, in claims 4 and 1 as originally filed. New claims 89 to 93 depend from claim 4, and are directed to a cDNA, vector, recombinant cells, method for expression, and method for modulating the level of apoptosis in a cell.

Claim 8 has been amended to indicate that the claimed oligonucleotide contains at least 500 nucleotides of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:5 or the complement thereof. Support

for this amendment to claim 8 can be found throughout the specification, for example, at page 13, lines 29-35.

Claim 27 has been amended to indicate that the method results in identifying a nucleic acid molecule encoding a mammalian NAC polypeptide that associates with SEQ ID NO:2 or with Apaf-1. Support for this amendment to claim 27 can be found throughout the specification, for example, at page 34, lines 16-24.

Claims 38 and 83 to 85 have been amended to recite methods of modulating the level of apoptosis in a cell *in vitro*. This amendment to claims 38 and 83 to 85 are supported in the specification, for example, at page 41, lines 31-34, which indicates that NAC nucleic acids can be delivered into mammalian cells *in vitro*. Claims 38 and 83 to 85 have also been amended to indicate that expression of the NAC modulates Apaf-1-mediated apoptosis in the cell. This amendment to claims 38, and 83 to 85 is supported in the specification, for example, at page 11, lines 6-22, which indicates that Apaf-1 activates caspase-9 protease to induce apoptosis; in Figure 5, which shows that NAC binds to Apaf-1; at page 49, lines 19-24, which indicates that association of NAC with a NAC associated protein can be altered to modulate a biological process such as the level of apoptosis in a cell; and at page 80, line 33, to page 81, line 1, which indicates that four indicators of protein:protein interaction confirmed that NAC interacts with Apaf-1.

Claims 70 and 75 have been rewritten in independent form. The amendments to claims 70 and 75 are supported for example, by claim 1 as originally filed.

Claim 77 has been amended to indicate the oligonucleotide comprises a nucleotide sequence consisting of nucleotides 985-1641 of SEQ ID NO:1 or its complement, or a fragment thereof consisting of at least 500 contiguous nucleotides therefrom and nucleotides at the 5' or 3' end that differ from SEQ ID NO:1 or its complement. The amendment to claim 77 is supported in the specification, for example, at page 35, lines 12-20, which indicates that a sequence of contiguous bases set forth in SEQ ID NO:1 can contain at least 500 contiguous bases.

Claim 78 has been amended to indicate that the oligonucleotide comprises a nucleotide sequence consisting of nucleotides 2422-2844 of SEQ ID NO:1 or its complement and nucleotides at the 5' or 3' end that differ from SEQ ID NO:1 or its complement. The amendment to claim 78 is supported in the specification, for example, in claim 8 as originally filed and at page 15, lines 28-31, which indicates that the LRR domain of NAC corresponds to amino acid residues 808-948 of SEQ ID NO:2 (i.e. nucleotides 2422-2844 of SEQ ID NO:1).

Claim 79 has been amended to indicate that the oligonucleotide comprises a nucleotide sequence consisting of nucleotides 3235-3960 of SEQ ID NO:1 or its complement and nucleotides at the 5' or 3' end that differ from SEQ ID NO:1 or

its complement. The amendment to claim 79 is supported in the specification, for example, in claim 8 as originally filed and at page 17, lines 4-7, which indicates that the TIM-Barrel-like domain of NAC corresponds to amino acid residues 1079-1320 of SEQ ID NO:2 (i.e. nucleotides 3235-3960 of SEQ ID NO:1).

Claim 80 has been amended to indicate that the oligonucleotide comprises a nucleotide sequence consisting of nucleotides 2870-2959 of SEQ ID NO:1 or its complement and nucleotides at the 5' or 3' end that differ from SEQ ID NO:1 or its complement. The amendment to claim 80 is supported in the specification, for example, in claim 8 as originally filed and at page 21, lines 3-21, which indicates that alternatively spliced exons of NAC correspond to nucleotides 2870-2959 and nucleotides 2870-2959 of SEQ ID NO:1.

Claim 81 has been amended to indicate that the oligonucleotide comprises a nucleotide sequence consisting of nucleotides 4117-4419 of SEQ ID NO:1 or its complement and nucleotides at the 5' or 3' end that differ from SEQ ID NO:1 or its complement. The amendment to claim 81 is supported in the specification, for example, in claim 8 as originally filed and at page 12, lines 21-24, which indicates that the CARD domain of NAC corresponds to amino acid residues 1373-1473 (i.e. nucleotides 4117-4419 of SEQ ID NO:1).

Claim 82 has been amended to indicate that the oligonucleotide contains at least 100 contiguous nucleotides of the nucleotide sequence set forth as nucleotides 3784-3915 of SEQ

ID NO:1 or its complement. The amendment to claim 82 is supported in the specification, for example, at page 35, lines 13-20, which indicates that a sequence of contiguous bases set forth in SEQ ID NO:1 can contain at least 100 contiguous bases, and in claim 8 as originally filed.

New claims 89 to 93 depend from claim 4, and are parallel to pending claims 5 to 7, 18 and 27. New claims 89 to 93 are supported, for example, by claims 5 to 7, 18 and 27 as originally filed.

New claims 94 to 98 depend from claim 70, and are parallel to pending claims 5 to 7, 18 and 27. New claims 94 to 98 are supported, for example, by claims 5 to 7, 18 and 27 as originally filed. New claims 93, 94 and 95 also are supported in the specification, for example, at page 41, lines 31-34.

New claim 99 is directed to a functional fragment of an isolated nucleic acid molecule that contains a nucleotide sequence set forth in either of SEQ ID NOs:3 or 5, the fragment containing a nucleotide sequence encoding a CARD domain corresponding to amino acids 1128-1261 and 1306-1473 of SEQ ID NO:2, and associating with SEQ ID NO:2 or with Apaf-1. Support for new claim 99 can be found in the specification, for example, at page 17, lines 16-21; and page 18, lines 16-26.

New claim 100 is directed to an oligonucleotide consisting of nucleotides 985-1641 of SEQ ID NO:1 or its complement, or a fragment thereof consisting of at least 500

contiguous nucleotides therefrom. Support for new claim 100 can be found in the specification, for example, at page 14, lines 4-7, which indicates that the NB-ARC domain of NAC corresponds to amino acid residues 329-547 of SEQ ID NO:2 (i.e. nucleotides 985-1641 of SEQ ID NO:1).

New claim 101 is directed to an oligonucleotide consisting nucleotides 2422-2844 of SEQ ID NO:1 or its complement. Support for new claim 101 can be found in the specification, for example, at page 15, lines 28-31, which indicates that the LRR domain of NAC corresponds to amino acid residues 808-948 of SEQ ID NO:2 (i.e. nucleotides 2422-2844 of SEQ ID NO:1).

New claim 102 is directed to an oligonucleotide consisting of nucleotides 3235-3960 of SEQ ID NO:1 or its complement. Support for new claim 102 can be found in the specification, for example, at page 17, lines 4-7, which indicates that the TIM-Barrel-like domain of NAC corresponds to amino acid residues 1079-1320 of SEQ ID NO:2 (i.e. nucleotides 3235-3960 of SEQ ID NO:1).

New claim 103 is directed to an oligonucleotide consisting of nucleotides 2870-2959 of SEQ ID NO:1 or its complement. Support for new claim 103 can be found in the specification, for example, at page 21, lines 3-21, which indicates that alternatively spliced exons of NAC correspond to nucleotides 2870-2959 and nucleotides 2870-2959 of SEQ ID NO:1.

New claim 104 is directed to an oligonucleotide consisting of nucleotides 4117-4419 of SEQ ID NO:1 or its complement. Support for new claim 104 can be found in the specification, for example, at page 12, lines 21-24, which indicates that the CARD domain of NAC corresponds to amino acid residues 1373-1473 (i.e. nucleotides 4117-4419 of SEQ ID NO:1).

As set forth above, the amendments and new claims are supported by the specification and claims as originally filed, and do not introduce new matter. Accordingly, entry of the amendments and new claims is respectfully requested.

Attached hereto as Appendix A is a marked up version of the amendments, in which added text is underlined and deleted text is enclosed in brackets.

Regarding new independent claims

Applicant points out that claims 4, 70 and 75 have been rewritten in independent form. These claims are free of rejection and thus should be considered allowable. In addition, new claims 89 to 93, which depend from claim 4, and new claims 94 to 98, which depend from claims 70 and 75, have been added.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, written description

The objection to the specification and corresponding rejection of claims 1, 5 to 7, 18, 38, 66 to 69, 71 to 74 and 83

to 86 under 35 U.S.C. § 112, first paragraph, as allegedly lacking sufficient description of the claimed nucleic acids to convey to one skilled in the art that Applicant was in possession of the invention at the time of filing the application, are respectfully traversed.

The Office Action asserts that the claims under examination do not recite an isolated nucleic acid molecule encoding a polypeptide that contain an NB-ARC domain. On the contrary, Applicant respectfully points out that claims 1 and 71 both recite an isolated nucleic acid molecule encoding "a NB-ARC and CARD containing protein" in the claim preamble. Nevertheless, as amended herein, claims 1 and 71 now both recite the phrase "wherein said polypeptide comprises an NB-ARC domain" in the claim body. Therefore, Applicant submits that claims 1 and 71 and dependent claims 5 to 7, 18, 38, 66 to 69, 72 to 74 and 83 to 86 are directed to nucleic acid molecules that contain both CARD and NB-ARC domains, and to fragments thereof.

The Office Action asserts that the specification does not provide description of the functional activity of NAC nucleotide sequences that would distinguish NAC nucleotide sequences, such as NAC nucleotide sequences that encoded polypeptides with 80% or greater identity with SEQ ID NOS:2, 4, or 6, from a nucleic acid molecule that encodes "simply a protein capable of binding to a CARD domain."

On the contrary, Applicant respectfully submits that the specification describes multiple functional characteristics

of NACs that would characterize NACs encoded by SEQ ID NOS:2, 4 and 6 and highly related sequences, and that would distinguish the claimed nucleotide sequences from those encoding unrelated proteins. In particular, the specification teaches that a NAC can associate with another cellular NAC, such as NACβ (SEQ ID NO:2), and that this association is mediated, independently, by CARD and the NB-ARC domains (page 12, line 31, to page 13, line 7 and page 14, lines 11-15). Therefore, functional characteristics of CARD and NB-ARC domains of a NAC polypeptide can be independently assessed. One skilled in the art knows how to determine if a nucleic acid molecule encodes a polypeptide having both CARD and NB-ARC domains, for example, by confirming independently the ability of each of these domains to bind to a cellular NAC, such as NACβ (SEQ ID NO:2), as recited in claims 1 and 7. Given the description in the specification of the structural and functional features of CARD and NAC domains, these domains would have been readily distinguished from "simply a protein capable of binding to a CARD domain." Therefore, Applicant submits that the specification provides sufficient description of the functional activity of CARD and NB-ARC domains of a NAC to demonstrate that Applicant was in possession of the claimed nucleic acid molecules rather than a nucleic acid molecule that encodes "simply a protein capable of binding to a CARD domain."

Regarding *in vitro* and *in vivo* activity of NAC polypeptides

The Office Action asserts that demonstration of binding to an NB-ARC or CARD domain *in vitro* does not demonstrate that a

NAC protein naturally binds proteins containing these domains *in vivo* or that the binding results in any particular biological activity in a cell. In this regard, the Examiner has not acknowledged the cellular activity of NAC polypeptides as described in Chu et al., J. Biol. Chem. 276:9329-9245 (2001), submitted as Exhibit A in the response filed August 29, 2002, but requests confirmation that the NAC polypeptide sequences described in Chu et al. are the same as those referenced as SEQ ID NOS: 2, 4 or 6. Applicant respectfully submits that the NAC polypeptide sequences described in Chu et al. Figure 1B are the same as those referenced as SEQ ID NOS:2, 4 and 6 in the present application (compare, for example, Figure B of Chu et al. and Figure 1C of the specification). As previously described on the record, Chu et al. corroborates *in vitro* activity disclosed in the specification by showing that NAC polypeptide (SEQ ID NO:2) and fragments thereof have the expected cellular functional activity.

In view of the above, Applicant submits that claims 1, 5 to 7, 18, 38, 66 to 69, 71 to 74 and 83 to 86 are supported by sufficient description in the specification to convey to one skilled in the art that Applicant had possession of the claimed invention at the time of filing the application.

Regarding the rejection under 35 U.S.C. § 112, first paragraph, enablement

The objection to the specification and corresponding rejection of claims 1, 5 to 7, 18, 38, 66 to 69, 71 to 74 and 83

to 86 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement in the specification, are respectfully traversed.

The Office Action acknowledges that the specification is enabling for an isolated nucleic acid molecule referenced as SEQ ID NO:1, 3 or 5, which encode amino acid sequences SEQ ID NO:2, 4 or 6. However, the Office Action alleges that the specification lacks enablement for functional fragments, nucleic acid molecules that hybridize to NAC oligonucleotides under high stringency conditions, degenerate nucleotide sequences, or methods of modulating the level of apoptosis in a cell by introducing a NAC nucleic acid molecule into a cell.

The Office Action asserts that claims 1, 5 to 7, 18, 38, 66 to 69, 71 to 74 and 83 to 86 lack enablement in the specification because the demonstration of binding of an NB-ARC or CARD domain *in vitro* does not demonstrate that a NAC naturally binds to target proteins *in vivo* or that the binding results in any particular biological activity in any type of cell in a mammal. In regard to claims that recite nucleic acid molecules and fragments thereof (claims 1, 5 to 7, 18, 66 to 69, 71 to 74 and 86), Applicant submits that the claims do not recite a particular *in vivo* activity. Rather, claims directed to NAC nucleic acid molecules recite encoded polypeptides having specific structural features (at least 80% identity to SEQ ID NO:4 or SEQ ID NO:6; a CARD domain fold; an NB-ARC domain) and functional features (associates with SEQ ID NO:2 or with Apaf-1). Therefore, Applicant respectfully submits that demonstration of a

particular *in vivo* activity is not required for enablement of claims 1, 5 to 7, 18, 66 to 69, 71 to 74 and 86.

In regard to claims directed to methods of modulating the level of apoptosis in a cell (claims 38, and 83 to 85), Applicant has previously submitted post-filing reference Chu et al., which confirms the ability of NAC (SEQ ID NO:2) to associate with Apaf-1 taught in the specification and further confirms that this activity translates to modulation of apoptosis in a cell. Chu et al. also confirms the ability of the individual CARD and NB-ARC domains of NAC to associate, as taught in the specification, as well as confirms the ability of these domains to modulate apoptosis in a cell (see, for example, Chu et al., page 9239, abstract). As amended, claims 38, and 83 to 85 are directed to introducing into a cell *in vitro* an isolated nucleic acid molecule that encodes a NAC having specific structural features (at least 80% identity to SEQ ID NO:4 or SEQ ID NO:6; a CARD domain fold; an NB-ARC domain) and functional features (associates with SEQ ID NO:2 or with Apaf-1) to modulate Apaf-1-mediated apoptosis. Based on the description in the specification of the ability of a polypeptide encoded by SEQ ID NO:2, 4 or 6, or fragment thereof, to bind *in vitro* to apoptosis regulator molecule Apaf-1 (for example, page 76, line 9, to page 81, line 20), and the confirmatory description in Chu et al. of the ability of a NAC polypeptide encoded by SEQ ID NO:2, or a fragment thereof, to bind to Apaf-1 and modulate apoptosis in a cell, those skilled in the art would have been able to use a NAC nucleic acid molecule to modulate Apaf-1-mediated apoptosis in a variety of cell types without undue experimentation.

Regarding gene therapy

The Office Action asserts that introducing a nucleic acid molecule into a cell *in vivo*, i.e. gene therapy, is unpredictable and therefore that methods of the invention practiced *in vivo* lack enablement in the specification. Applicant maintains for reasons of record that introducing a NAC nucleic acid molecule into a cell of a living subject is enabled by the specification. Nevertheless, claims 38 and 83 to 85 have been amended to indicate that a NAC nucleic acid molecule is introduced into a cell outside of a living subject (*in vitro*). Applicant submits that claims 38 and 83 to 85 as amended are enabled by the specification and that which was known to those skilled in the art at the time of filing the present application. For example, the specification provides guidance for introducing a NAC nucleic acid molecule into several different cell types *in vitro*. In particular, the specification discloses introducing a NAC nucleic acid molecule or fragment thereof into human embryonic kidney fibroblast (HEK) cells *in vitro* (page 83, lines 16-34). Further disclosed is that NAC polypeptides expressed in HECK cells have functional activity as evidenced, for example, by the ability of the polypeptides to bind to Apaf-1 in the cell (page 84, lines 16-32). Moreover, as described in Chu et al., Figure 4E, introduction of full-length NACβ (SEQ ID NO:2) into 293T cells resulted in enhanced apoptosis. Therefore, Applicant respectfully submits that claims 38, and 83 to 85, as well as new claims 93 to 98, directed to modulating the level of apoptosis in a cell *in vitro* are enabled in the specification.

Regarding NAC nucleic acid molecules encoding polypeptides having point mutations with respect to defined sequences

The Office Actions asserts that nucleic acid molecules that encode NAC polypeptides other than those having SEQ ID NOS:2, 4 and 6 are not enabled by the specification because a single nucleotide or amino acid change or mutation can destroy or substantially change the function of a biomolecule. As support for this statement, the Examiner cites Ding et al., which describes a substitution of an alanine with isoleucine in IL-10 that significantly affects IL-10 affinity for its receptor. Applicant respectfully submits that CARD and NB-ARC domains of NAC polypeptides are dissimilar and unrelated to chemokines, which are characterized by multiple highly conserved cysteine residues. Therefore, a single amino acid mutation in IL-10 is not predictive of the effect of such a mutation on a NAC polypeptide.

Moreover, using guidance provided in the specificaition for selecting nucleotides and amino acids that are tolerant of substitution, one skilled in the art would have been able to predict amino acid residues that are likely to be tolerant or intolerant of substitution. The specification provides, for example, comparisons of multiple CARD and NB-ARC domain sequences (Figures 1D and 1E) useful for this purpose. Further, the specification provides assays for determining functional activity of a NAC such that one skilled in the art would have been able to test point mutants without undue experimentation (see, for example, pag 78, line 11, to page 84, line 32). In view of this

guidance in the specification, Applicant submits that the specification provides sufficient guidance for one skilled in the art to predict whether a single amino acid change would result in a polypeptide or fragment thereof with identical function to the original protein, as well as for one skilled in the art to test a point mutant for the recited functional activity.

In view of the above amendments and arguments, Applicant respectfully submits that claims 1, 5 to 7, 18, 38, 66 to 69, 71 to 74 and 83 to 86 are enabled in the specification. Therefore, removal of this rejection under 35 U.S.C. § 112, first paragraph, is respected requested.

Regarding the rejection under 35 U.S.C. § 112, second paragraph

The rejection of claims 8, 9, 11, 27, 77 to 81, 87 and 88 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite, is respectfully traversed. The Office Action alleges that claims directed to oligonucleotides that consist of particular nucleotide sequences and optionally contain additional nucleotides are indefinite.

Applicant maintains that claims 8, 9, 11, 27, 77 to 81, 87 and 88 are clear and definite as written. In particular, one skilled in the art would have understood the use of "closed language" to describe oligonucleotides that contain both a defined region of specified nucleotide sequence, and a region of unrelated sequence at the 5' or 3' end. Nevertheless, as amended herein, claims 8 and 77 to 81 recite oligonucleotides that

comprise a nucleotide sequence consisting of contiguous nucleotides of a recited nucleotide sequence, and a nucleotide sequence at the 5' or 3' end that differs from the recited nucleotide sequence. Applicant submits that claims 8 and 77 to 81, as amended, are clear and definite. Therefore, removal of this rejection under 35 U.S.C. § 112, second paragraph, is respected requested.

Regarding the rejections under 35 U.S.C. § 102(b)

The rejection of claim 8 under 35 U.S.C. § 102(b), as allegedly anticipated by GSS sequence submission B33808 is respectfully traversed. The Office Action asserts that GSS submission B33808 contains 420 contiguous nucleotides that are identical to SEQ ID NO:1 nucleotides 1882-2301.

As amended herein, claim 8 is directed to an oligonucleotide that contains at least 500 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or of the complement thereof. GSS sequence submission B33808 does not teach an oligonucleotide containing at least 500 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or the complement thereof. Therefore, it respectfully submitted that the cited reference does not anticipate claim 8, and Applicant respectfully requests removal of this rejection.

The rejection of claim 82 under 35 U.S.C. § 102(b), as allegedly anticipated by EST sequence submission H51863 is respectfully traversed. The Office Action asserts that EST

sequence submission H51863 contains 74 contiguous nucleotides that are identical to SEQ ID NO:1 nucleotides 3784-3860.

As amended herein, claim 82 is directed to an oligonucleotide that contains at least 100 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or of the complement thereof. EST sequence submission H51863 does not teach an oligonucleotide containing at least 100 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or the complement thereof. Therefore, it respectfully submitted that the cited reference does not anticipate claim 82, and Applicant respectfully requests removal of this rejection.

Regarding the rejection under 35 U.S.C. § 103

The rejection of claim 8 under 35 U.S.C. § 103(a), as allegedly obvious over Nagase et al. DNA Res. 6:63-70 (1999) in view of Nagase et al. DNA Res. 5:277-286 (1998), is respectfully traversed.

The Office Action alleges that the description in Nagase (1999) of a cDNA sequence referenced by accession number and description in Nagase (1998) of the use of primers for detecting mRNA expression in cells together render obvious claim 8.

As amended herein, claim 8 is directed to an oligonucleotide contains at least 500 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5, or the complement thereof.

The description of 21mer oligomers in the combination of cited references provides no teaching or suggestion of oligonucleotides comprising at least 500 nucleotides up to 1035 nucleotides of SEQ ID NOS:1, 3 or 5. For this reason, it respectfully submitted that the cited references in combination do not render obvious claim 8.

In view of the above amendments and remarks, reconsideration and removal of the rejection of claim 8 under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

In light of the amendments and remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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APPENDIX A

1. (Four Times Amended) An isolated nucleic acid molecule encoding a NB-ARC and CARD containing protein (NAC), comprising a nucleotide sequence encoding a polypeptide having at least 80% identity to SEQ ID NO:4 or SEQ ID NO:6, or the complement of said nucleotide sequence,

wherein said polypeptide forms a CARD domain fold,

wherein said polypeptide comprises an NB-ARC domain capable of associating with the NB-ARC domain of SEQ ID NO:2,

wherein said polypeptide does not comprise amino acids 957-987 of SEQ ID NO:2, and

wherein said polypeptide associates with SEQ ID NO:2 or with Apaf-1.

4. (Amended) **An isolated nucleic acid molecule encoding a NB-ARC and CARD containing protein (NAC), comprising a nucleotide sequence [A nucleic acid molecule according to claim 1, wherein the nucleotide sequence of said nucleic acid molecule is the same as that]** set forth in either of SEQ ID NOs:3 or 5.

8. (Three Times Amended) An oligonucleotide consisting of at least **[30] 500** contiguous nucleotides up to 1035 contiguous nucleotides of the nucleotide sequence set forth in any of SEQ ID Nos: 1, 3 and 5 or the complement of said nucleotide sequence, **[said olignucleotide optionally having additional nucleotides] and a nucleotide sequence** at the 5' or 3' end that **[differ] differs** from the nucleotide sequence set forth in any of SEQ ID Nos: 1, 3 and 5 or the complement of said nucleotide sequence.

27. (Twice Amended) A method for identifying **a** nucleic **[acids] acid molecule** encoding a mammalian NAC, said method comprising:

contacting a sample containing nucleic **[acids] acid molecules** with the oligonucleotide of any one of claims 77, 78, 79, 80, 81 or 82, wherein said contacting is effected under high stringency hybridization conditions, and identifying **[compounds which hybridize thereto] a nucleic acid molecule that hybridizes thereto, wherein said nucleic acid molecule encodes a mammalian NAC polypeptide that associates with SEQ ID NO:2 or with Apaf-1**.

38. (Twice Amended) A method of modulating the level of **Apaf-1-mediated** apoptosis in a cell ***in vitro***, comprising the steps of:

a) introducing a nucleic acid molecule encoding a NAC according to claim 1 into the cell ***in vitro***; and

b) expressing said NAC in said cell, wherein the expression of said NAC modulates **Apaf-1-mediated** apoptosis in said cell.

70. (Amended) **[The nucleic acid molecule of claim 1]** **An isolated nucleic acid molecule encoding a NB-ARC and CARD containing protein (NAC)**, comprising a nucleotide sequence encoding SEQ ID NO:4 or 6.

71. (Twice Amended) An isolated nucleic acid molecule encoding a NAC, comprising a nucleotide sequence encoding a polypeptide having at least 80% identity to SEQ ID NO:2, or the complement of said nucleotide sequence,

wherein said polypeptide comprises amino acids 1262-1305 of SEQ ID NO:2,

wherein said polypeptide forms a CARD domain fold, **[and]**

wherein said polypeptide comprises an NB-ARC domain capable of associating with the NB-ARC domain of SEQ ID NO:2, and

wherein said polypeptide associates with SEQ ID NO:2 or with Apaf-1.

75. (Amended) **[The nucleic acid molecule of claim 71]** **An isolated nucleic acid molecule encoding a NB-ARC and CARD containing protein (NAC)**, comprising a nucleotide sequence encoding SEQ ID NO:2.

77. (Twice Amended) An oligonucleotide **[consisting of the]** **comprising a** nucleotide sequence **[set forth as]** **consisting of** nucleotides 985-1641 of SEQ ID NO:1 or its complement, or a fragment thereof consisting of at least [20] 500 contiguous nucleotides therefrom, **[said oligonucleotide or fragment optionally having nucleotides]** **and a nucleotide sequence** at the 5' or 3' end that **[differ]** **differs** from SEQ ID NO:1 or its complement.

78. (Twice Amended) An oligonucleotide **[consisting of the]** **comprising a** nucleotide sequence **[set forth as]** **consisting of** nucleotides 2422-2844 of SEQ ID NO:1 or its complement, or a fragment thereof consisting of at least 20 contiguous nucleotides

therefrom, **[said olignucleotide or fragment optionally having nucleotides]** **and a nucleotide sequence** at the 5' or 3' end that **[differ]** **differs** from SEQ ID NO:1 or its complement.

79. (Twice Amended) An oligonucleotide **[consisting of the]** **comprising a** nucleotide sequence **[set forth as]** **consisting of** nucleotides 3235-3960 of SEQ ID NO:1 or its complement, **[or a fragment thereof consisting of at least 20 contiguous nucleotides therefrom, said olignucleotide or fragment optionally having nucleotides]** **and a nucleotide sequence** at the 5' or 3' end that **[differ]** **differs** from SEQ ID NO:1 or its complement.

80. (Twice Amended) An oligonucleotide **[consisting of the]** **comprising a** nucleotide sequence **[set forth as]** **consisting of** nucleotides 2870-2959 of SEQ ID NO:1 or its complement, **[or a fragment thereof consisting of at least 20 contiguous nucleotides therefrom, said olignucleotide or fragment optionally having nucleotides]** **and a nucleotide sequence** at the 5' or 3' end that **[differ]** **differs** from SEQ ID NO:1 or its complement.

81. (Twice Amended) An oligonucleotide **[consisting of the]** **comprising a** nucleotide sequence **[set forth as]** **consisting of** nucleotides 4117-4419 of SEQ ID NO:1 or its complement, **[or a fragment thereof consisting of at least 20 contiguous nucleotides therefrom, said olignucleotide or fragment optionally having nucleotides]** **and a nucleotide sequence** at the 5' or 3' end that **[differ]** **differs** from SEQ ID NO:1 or its complement.

82. (Amended) An oligonucleotide comprising at least **[20]** **100** contiguous nucleotides of the nucleotide sequence set forth as nucleotides 3784-3915 of SEQ ID NO:1 or its complement.

83. (Amended) A method of modulating the level of **Apaf-1-mediated** apoptosis in a cell ***in vitro***, comprising the steps of:

a) introducing a nucleic acid molecule encoding a NAC according to claim 71 into the cell ***in vitro***; and
b) expressing said NAC in said cell, wherein the expression of said NAC modulates **Apaf-1-mediated** apoptosis in said cell.

84. (Amended) A method of modulating the level of **Apaf-1-mediated** apoptosis in a cell ***in vitro***, comprising the steps of:

a) introducing a nucleic acid molecule encoding a NAC functional fragment according to claim 66 into the cell ***in vitro***; and

b) expressing said NAC functional fragment in said cell, wherein the expression of said NAC functional fragment modulates **Apaf-1-mediated** apoptosis in said cell.

85. (Amended) A method of modulating the level of **Apaf-1-mediated** apoptosis in a cell ***in vitro***, comprising the steps of:

a) introducing a nucleic acid molecule encoding a NAC functional fragment according to claim 86 into the cell ***in vitro***; and

b) expressing said NAC functional fragment in said cell, wherein the expression of said NAC functional fragment modulates **Apaf-1-mediated** apoptosis in said cell.

Two Small Entity Statements

Attorney Docket No.: 66654-010 (P-LJ 3650)
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on March 6, 2003.

By Pamela M. Guy
Pamela M. Guy, Reg. No. 51,228

March 6, 2003
Date of Signature